NCN-Pincer-Pd Complex as Catalyst for the Hiyama Reaction in Biomass-Derived Solvents

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ABSTRACT

A NCN-pincer-Pd complex have been synthetized and applied to Hiyama-type cross-coupling reactions between aryl halides and different types of organosilanes using neoteric solvents. This report constitutes a green approach to cross-coupling reactions since the reagents employed are stable and non-toxic. The solvents used (Deep Eutectic Solvents based on choline chloride or glycerol) are also biodegradable, non-toxic, non-flammable and biorenewable. Furthermore, the catalytic system can be recycled, allowing to perform the reaction for at least three cycles without adding more catalyst or solvent, increasing the value of the process from an economical and environmental point of view. The effect of these solvents on the catalytic activity has been studied. Finally, a gram-scale reaction has also been tested affording biaryl products in high yields and purity by a simple liquid-liquid extraction, without the need of aqueous work-up or chromatographic steps, proving the applicability of this approach in a sustainable industrial scale.

KEYWORDS

Green Chemistry; Organometallics; Deep eutectic solvents; Cross-coupling.

Introduction

Cross-coupling reactions have emerged as a fundamental tool for the C-C bond formation, this has been recognized by the fact that several Nobel Prizes have been awarded in this area over the last years.[1] This kind of reactions are usually performed under metallic catalysis, the most used metals being: Pd,[2-3] Cu,[4-5] Fe,[6-7] Ni[8-9] or Zn.[10-11]The metal that has been more broadly applied in cross coupling reactions is Pd, due to its high selectivity, reactivity and tolerance to a broad scope of functional groups.[12] Reactions such as the Suzuki, Heck or Sonogashira couplings often take place under classical Pd (0)/Pd (II) catalytic cycle,[3] although there are some reports regarding the use of Pd (II)/Pd (IV) species.[13]

These cross-coupling reactions permit the synthesis of relatively complex molecules, forming carbon-carbon or carbon-heteroatom bonds in a simple way. This approach has been applied in several processes, both in industry and academia.[14] Due to its importance and large applicability, finding a sustainable way to carry out these reactions is a matter to be urgently addressed.

Within this context, Green Chemistry has emerged as a manner to deal with traditional chemistry's environmental problems by proposing 12 principles that every chemical process should follow.[15] According to its third principle, less hazardous chemicals should be used when preparing a synthetic plan. In this matter, Hiyama reaction stands out among other cross-coupling reactions, since it is based in the use of organosilicon reagents. These kind of chemicals are usually very stable against air and moisture,[16] they are non-toxic, environmentally-friendly and are commercially available at low cost or easily prepared.[17]

Another aspect to be considered is the use of solvents. Although from an environmentally point of view, it is considered that the best solvent is its absence,[18-19] the use of a solvent is normally required to stabilize the catalyst, to obtain a homogeneous mixture, or to favor the heat or mass transfer process. For this reason, instead of using VOC solvents (Volatile Organic Compounds), which generate loads of toxic, flammable waste, and have a great carbon footprint; biorenewable compounds should be considered as reaction media.[20-21] In this context, deep eutectic solvents (DESs) are an outstanding choice, since they are formed by mixing two or more inexpensive, non-toxic, and usually biorenewable compounds, such as choline chloride (an inexpensive food additive) or glycerol (a biodiesel industry by-product). Most of the components of DES are considered harmless and biodegradable,[22] which added to the fact that they are non-flammable, makes them a good choice as alternative reaction media for organic transformations.[23-24]

Some approaches to the Hiyama coupling in neoteric solvents include the use of water as reaction medium, usually under reflux conditions, using phase transfer catalyst or with highly activated starting materials, such as diazonium salts.[25-29] Ionic liquids, which share some of the advantages of DES, but with the drawbacks of being highly toxic and economically expensive, have also been recently investigated as reaction medium. A Hiyama-type reaction in ionic liquids was described by Bäuerlein et al, using 10 mol% of a Pd precursor, 20 mol% of a complex ligand and 4 equivalents of a fluoride salt.[30] Another report in this kind of solvent employed 4 mol% of Pd without any additives, but required instead the use of an expensive ionic liquid containing fluoride anions. Also, MeCN was used as co-solvent, in which case, the problematic use of VOC as solvent was not avoided.[17]

Among neoteric alternatives, biorenewable solvents are attracting more interest in recent years.[31-33] Hiyama coupling have been performed in γ-valerolactone,[34] and more recently in glycerol, although to the best of our knowledge only one report of this coupling reaction have been published in this medium so far.[35] In this case, 2 mol % of Pd (0) nanoparticles preformed from $Pd(OAc)_2$ and a phosphine ligand, were used as catalyst for the reaction. Only 6 biaryl products were obtained, showing uncontrolled selectivity towards homocoupling by-products, which are difficult to separate from the corresponding cross-coupling products, increasing the negative impact on the sustainability of the whole process (Fig 1).

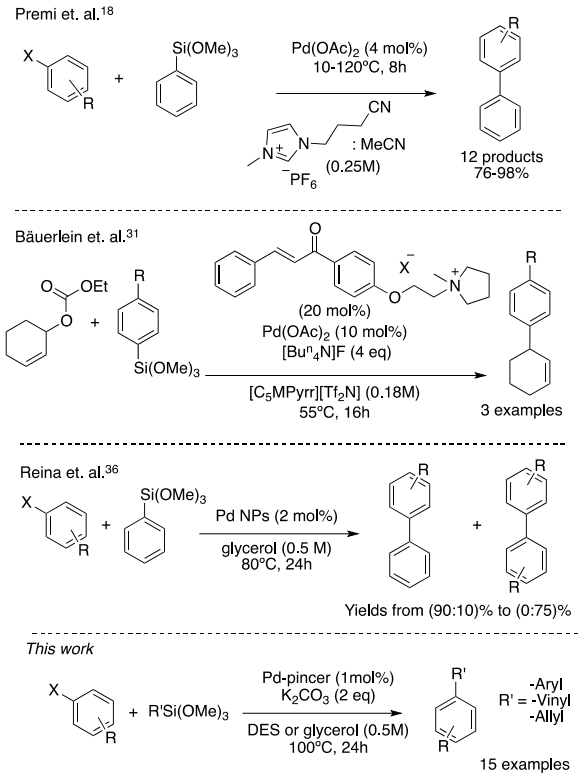


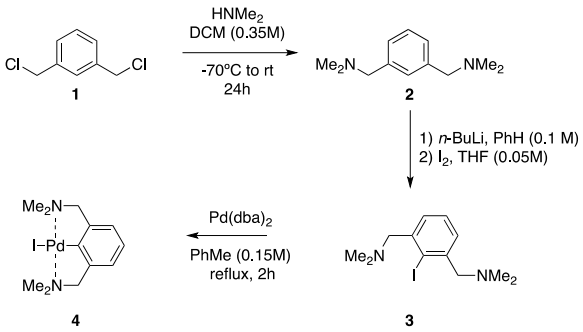
Figure 1. Hiyama-type reaction in neoteric solvents.

One of the most interesting aspects of using neoteric solvents is the possibility of immobilizing the catalyst, which allows the recyclability of the system. Nevertheless, this recycling process have not been described for the Hiyama-type reaction in the aforementioned reports (Fig. 1).

Results and discussion

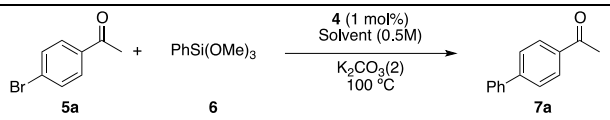
With these precedents, our aim was to develop a recyclable catalytic system based on a Pd complex able to catalyze the Hiyama reaction. This goal could be achieved taking advantage of the properties of neoteric solvents such as DES. For this purpose, we thought that a highly stable pincer-type palladium complex might be a good candidate for catalyst. Catalyst **4** was synthetized following a literature procedure[36-37] (Scheme 1).

Scheme 1. Catalyst synthesis.



Organometallic complex **4** was tested as catalyst for the reaction between 4'-bromoacetophenone (**5a**) and trimethoxyphenylsilane (**6**), employing different DESs as reaction mediums. A study to determine the optimal reaction conditions was performed. Different amounts of each of the reagents, several bases, different temperatures and nearly 20 different eutectic mixtures were tested (Table S1). The reaction failed in most of the employed DES, although 70% yield was obtained in ChCl:glycerol (1:2) and 25% yield in ChCl:ethylene glycol (1:2) (Table 1, entries 1-2). The reaction was also tested in neat ethylene glycol and glycerol, obtaining yields of 72 and 89%, respectively (entries 3-4). Toluene, a traditional VOC solvent, was also employed as reaction media, as well as neat conditions, obtaining low conversions in both cases (entries 5-6). This fact highlights the role of neoteric solvent, enhancing the catalytic activity of the system.

Table 1. Selected results from reaction optimization.

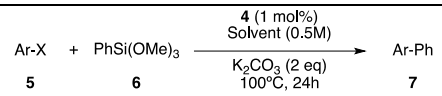


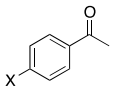
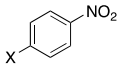
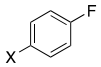
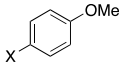
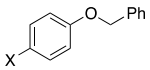
Entry	Solvent	Yield (%)[a]
1	ChCl:glycerol (1:2)	70
2	ChCl:ethylene glycol (1:2)	25
3	Glycerol	89
4	Ethylene glycol	72
5	Neat conditions	12
6	Toluene	23

[a] Yield determined by GC using tridecane as internal standard.

After having optimized the reaction conditions, the scope of the reaction was analyzed with different aryl halides, using DES and glycerol as solvent. In the case of using ChCl:glycerol (1:2) as reaction media, moderate to low yields were obtained for aryl halides bearing electron-withdrawing groups (Table 2, entries 1-3) or electron-neutral aryl halides (Table 2, entries 4, 8) In the case of using electron-rich aryl halides, the reaction yields were slightly lower (entries 5-7). The scope of aryl halides was analyzed again using neat glycerol. In this case, moderate to excellent yields were obtained for aryl bromides and iodides bearing both, electron-withdrawing and electron-donating groups (Table 2). It is worth to mention that no homocoupling byproducts were observed under the optimized reaction conditions, neither in DES nor in glycerol, as solvent.

Table 2. Scope of aryl halides[a]



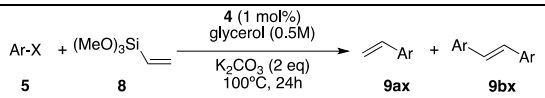
Entry	Substrate	X	Product	Yield in DES[b] (%)[c]	Yield in glycerol (%)[c]
1		Br	**7a**	70	89
		I		19	97
2		Br	**7b**	11	63
		I		3	65
3		Br	**7c**	35	88
4		Br	**7d**	85	62
		I		69	94
5		Br	**7e**	27	64
		I		58	80
6		Br	**7f**	1	40
		I		36	83
7		I	**7g**	58	75
8		Br	**7h**	77	80
		I		63	99

[a] Reaction conditions: Aryl halide (1 mmol), $PhSi(OMe)_3$ (1.5 mmol), K_2CO_3 (2 mmol), catalyst **4** (0.01 mmol) in 2 mL of solvent. [b] DES stands for ChCl:glycerol (1:2/molar ratio). [c]Isolated Yield.

Then, the vinylation reaction of aryl halides employing trimethoxyvinylsilane (**8**) was tested. In this case, the reaction worked with good to excellent yields for aryl iodides and bromides bearing electron-withdrawing functional groups, and with moderate yields with aryl iodides with electron-donating groups, including electron-rich heterocycles (Table 3, entries 11-12). The same

range of yields were obtained using glycerol and ChCl:glycerol (1:2) as solvent (Table 3). The reaction products, vinylbenzenes, sometimes suffer from a second Pd-catalyzed Heck-type reaction with the aryl halide to yield a 1,2-disubstituted ethene derivative (**9b**x).[38] The selectivity to these products could not be controlled, as it depends on the nature of the starting material, obtaining only the Hiyama-type product (entries 1-5) or the Heck reaction product in some cases (entries 6, 11-12). The use of additives, such as KF, did not improve the reaction yield.

Table 3. Vinylarenes derivatives.[a]

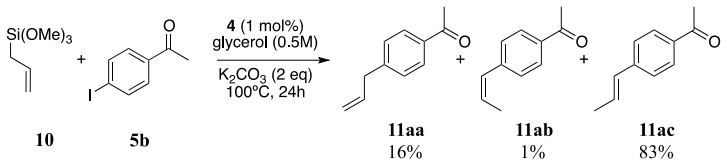


Entry	Ar	X	Product 9ax	Yield A (%)[b,c]	Product 9bx	Yield B (%)[b,c]
1	4-$MeCOC_6H_4$	Br	**9aa**	27 (60)	**9ba**	<1% (<1%)
2	4-$MeCOC_6H_4$	I	**9aa**	69 (75)	**9ba**	- (<1%)
3	4-$NO_2C_6H_4$	Br	**9ab**	51 (98)	**9bb**	- (-)
4	4-$NO_2C_6H_4$	I	**9ab**	89 (91)	**9bb**	- (-)
5	3-pyridil	Br	**9ac**	77 (52)	**9bc**	- (<1%)
6	4-FC_6H_4	I	**9ad**	- (-)	**9bd**	65 (23)
7	4-$MeOC_6H_4$	Br	**9ae**	63 (55)	**9be**	- (<1%)
8	4-$MeOC_6H_4$	I	**9ae**	54 (64)	**9be**	<1% (<1%)
9	C_6H_5	Br	**9af**	56 (-)	**9bf**	30 (34)
10	C_6H_5	I	**9af**	26 (-)	**9bf**	52 (74)
11	2-thienyl	Br	**9ag**	- (-)	**9bg**	44 (8)
12	2-thienyl	I	**9ag**	- (-)	**9bg**	32 (55)

[a] Reaction conditions: Aryl halide (1 mmol), H_2C=CH-$Si(OMe)_3$ (1.5 mmol), K_2CO_3 (2 mmol), catalyst **4** (0.01 mmol) in 2 mL of glycerol. [b]Yields determined by GC-MS using tridecane as internal standard.[c] Yields obtained using ChCl:Glycerol (1:2; 0.5M) as solvent in parenthesis.

The reaction was tested also with allyltrimethoxysilane (**10**) under the same reaction conditions as before. In this case, a mixture of products was obtained. The coupling reaction took place to introduce the allyl moiety, achieving an sp^2-sp^3 C-C- coupling. Nevertheless, an isomerization also occurred, obtaining a mixture of three possible isomers, with the more stable internal *trans* double bond being the major one (Scheme 2). Reaction between benzyl bromide and phenyltrimethoxysilane was also tested, obtaining only traces of product diphenylmethane.

Scheme 2. Hiyama-type coupling with allyltrimethoxysilane.



The recyclability of the process was studied next. The reaction between reagents **5a** and **6** was performed under optimized conditions using ChCl:glycerol (1:2) as solvent. Once the reaction was finished, the organics were extracted with 2-MeTHF, a VOC considered to be a green solvent.[39] The catalyst remained in the DES phase, while unreacted starting materials and products were extracted. Adding a fresh batch of reagents, allowed to run the reaction again without using more solvent or catalyst. The reaction gave the same range of yields for 3 cycles, starting to decrease gradually after that. The recyclability was also tested using neat glycerol as solvent, obtaining a gradual decrease in the yield after each cycle (Fig. 2). The 2-MeTHF phase was analyzed by ICP-MS, finding that 7.9% of the initial Pd loading was extracted alongside with the product when glycerol was used as solvent, while 16.5% leaching was observed in the case of using DES as medium. This leaching process is probably the main reason for the decreased yield observed during recyclability experiments.

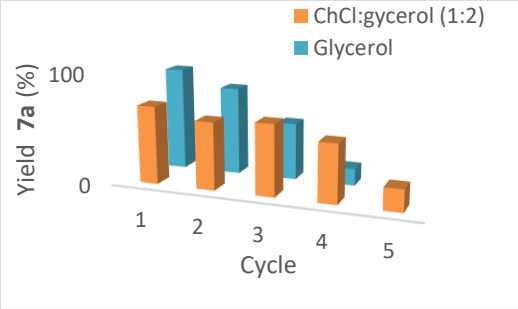
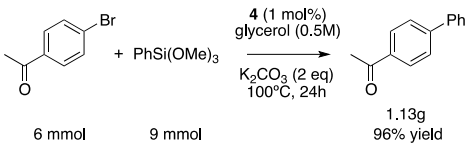


Figure 2. Recyclability study.

To prove the applicability of the process, the model reaction between 4-bromoacetophenone and $PhSi(OMe)_3$ was performed on a gram scale (Scheme 3). This reaction, was carried out with 12 mL of glycerol as solvent, stirred at 100ºC for 24h, cooled to room temperature and extracted with 2-MeTHF. The upper organic phase was evaporated to dryness and analyzed by ^1H NMR (see supporting information for details and pictures) to afford 1.13g of product **7a** (96% yield, 97% purity) without the need of aqueous work-up or chromatography purification (Fig. S2). The E-factor of this process was calculated, obtaining a value of 25.6, not being a high value for fine-chemical and pharmaceutical products industries.[40] This gram-scale reaction was also conducted in DES, obtaining only a 73% conversion to the desired product. However, a purification step was required to obtain the pure product, in contrast to the result obtained in glycerol as solvent.

Scheme 3. Gram-scale reaction. Isolated product in 96% yield without chromatography or aqueous work-up.



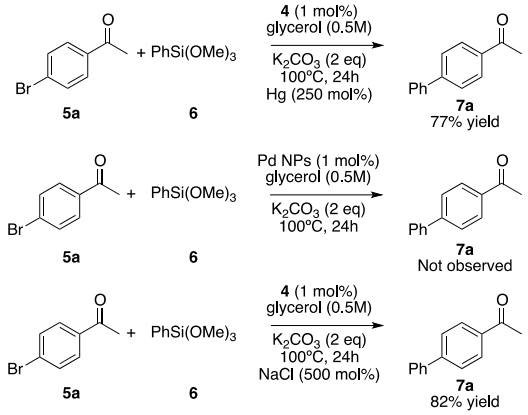
Regarding the mechanism of the reaction, it is believed to proceed *via* Pd (0)/ Pd (II) cycle according to literature precedents, and due to our previous experience in Pd chemistry in DES,[41] we analyzed the crude material by HRTEM trying to find Pd nanoparticles. Nevertheless, no

nanoparticles were found (neither in DES nor in glycerol as reaction medium) (Fig S1). The model reaction was also carried out using preformed Pd NPs (1 mol%) and no conversion at all was observed, recovering the unreacted starting material (Scheme 4). To confirm that the reaction was not being catalyzed by nanoparticles, a mercury test was performed in such a way that in the presence of Pd NPs, an amalgam with Hg would be formed, inhibiting its catalytic activity. The reaction was set up under standard conditions and a sample was analyzed by GC after 30 min of reaction time, observing a 11% conversion to desired product. Then, 250 mol% of Hg was added to the reaction mixture. After 24h, the reaction was worked-up and analyzed again, showing 77% yield. The obtained yield was slightly lower than the corresponding yield under optimized reaction conditions (89%), which may indicate that some Pd NPs are present in the reaction mixture, but they are not the main active catalytic species. Furthermore, the pincer complex could be isolated unchanged by column chromatography (in a 66 % yield). An XPS analysis of the crude material was also conducted. Despite of the low catalyst loading, the binding energy of Pd (II) species could be distinguished, but no Pd (0) was observed (Fig S2). These facts might suggest that this reaction in these kind of neoteric medium is probably occurring through the Pd (II)/ Pd (IV) catalytic system, which have been reported for similar pincer-type catalyst.[13]

Since, in general, better results were obtained in neat glycerol than in the corresponding eutectic mixture with ChCl, two control experiments were performed trying to decide if Cl^- anions could be occupying a vacant in the coordination sphere of the complex and thus, limiting its catalytic activity. The model reaction was carried out employing catalyst **4'**, bearing an Cl^- anion instead of an I^- (see ESI for details). The model reaction was also tested under standard conditions in glycerol but adding 5 equivalents of NaCl (Scheme 4). The yields for these two

tests were of 87% and 83%, respectively, quite similar to the standard result, being an indirect proof that Cl^- anions are not affecting the outcome of the reaction.

Scheme 4. Control experiments.



Conclusions

A NCN pincer Pd catalyst have been successfully applied to the Hiyama-type reaction in neoteric biomass derived solvents. Different organosilanes have been coupled with aryl halides using only 1 mol% of catalyst loading. The present work is the first report of a Hiyama reaction in DES and the first time in which the catalyst was recycled using glycerol as reaction media. The unique properties of the catalytic system based on the use of neoteric solvents, allows a greener approach to cross-coupling reactions compatible with sp^2- sp^2 and sp^2- sp^3 C-C bond. Although no direct evidence could be found, some proof suggests a possible Pd (II)/Pd (IV) cycle. Gram-scale approach is also feasible, obtaining biaryl product in high yield and purity without aqueous work-up or chromatographic steps, which, in addition to the use of biorenewable solvents and a recyclable catalyst, makes this a green approach to cross-coupling reactions.

Materials and methods.

General procedure 1. Hiyama-type reaction.

To a solution of aryl halide (1.0 mmol), potassium carbonate (2 mmol), catalyst **4** (0.01 mmol) in 2 mL of DES or glycerol, 1.5 mmol of organosilane was added and the resulting mixture was stirred for 24h at 100°C. The mixture was quenched with water and extracted with EtOAc (3 x 5 ml). The combined organic phases were dried over $MgSO_4$, followed by evaporation under reduced pressure to remove the solvent. Products were usually purified by chromatography on silica gel (hexane/ethyl acetate) and/or distillation to give the corresponding products. Physical and spectroscopy data, as well as the literature for known compounds are given in the supporting information.

General procedure for recycling experiments.

Reaction was performed according to general procedure **1**. Once the reaction was completed, the reaction mixture was cooled to room temperature and 2-MeTHF was added to the reaction vessel. The biphasic mixture was stirred for 5 min and the upper phase was separated by decantation and analyzed by GC using tridecane as internal standard. The DES or glycerol phase was dried under vacuum and was charged again with fresh reagents and base, repeating the process.

ASSOCIATED CONTENT

Supporting Information. Electronic supplementary information (ESI) available: characterization data, TEM images, XPS, ^{1}H-NMR and ^{13}C-NMR data (PDF).

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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ABBREVIATIONS

ChCl, choline chloride; DES, deep eutectic solvent; TEM, transmission electron microscopy.

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SYNOPSIS. A green approach to Hiyama cross-coupling reaction have been performed using a Pd-NCN-pincer complex in biorenewable solvents.

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